REMARKS

Reconsideration and allowance are respectfully requested.

Claims 23, 33-41, 44 and 49-54 are pending. The amendments are supported by the original disclosure and, thus, no new matter is added by their entry. Here, the independent claim is amended by incorporating features of claims 25 and 28. Claims 24-28 and 45-48 are canceled because they are redundant in view of amended claim 23. Claims 33, 36-37 and 40-41 are amended such that they conform to the scope of the independent claim. Methods for using the fusion protein are split into claims 33 and 54.

Non-elected claims 33-36, 40-41 and 49-54 are withdrawn from consideration by the Examiner. Applicants request rejoinder of the withdrawn claims upon allowance of an elected product claim. Withdrawn claims 42-43 are also canceled because they are redundant in view of amended claim 40.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner related subject matter in the U.S. patent applications, Serial Nos. 10/380,002, 10/557,586, and 12/933,390. The Examiner is invited to consider their prosecution histories and the prior art of record in those applications, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if she prefers.

Statement of the Substance of the Interview

A telephonic interview with the Examiner was conducted on February 11, 2011. The undersigned discussed the possibility of specifying the fusion protein comprised the amino acid sequence of SEQ ID NO: 4. No agreement was reached, but it appeared that the aforementioned amendment would reduce issues being controverted. The fore-

going is Applicants' summary of the interview. If anything else is required to complete the record, do not hesitate to contact the undersigned.

Double Patenting

Claims 23-28, 37-39 and 44-48 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 29-33 of copending application, Serial No. 10/557,586 in view of Colombo et al. (J. Immunol. 160:2780-2785, 1998) and Colombo et al. (Int'l Arch. Allergy Immunol., 130:173-179, 2003). Applicants traverse because the '586 application is abandoned.

Withdrawal of the provisional double patenting rejection is requested.

35 U.S.C. 112 – Definiteness

Claims 23-28, 37-39 and 44-48 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Addition of a sequence identifier (SEQ ID NO: 4) moots this rejection.

Therefore, Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 23-28, 37-39 and 44-48 were rejected under Section 112, first paragraph, because the specification allegedly does not reasonably provide enablement for the full scope of the claimed invention. Applicants traverse.

The present claims require a fusion protein characterized in that it comprises the amino acid sequence SEQ ID NO: 4. Previously, the Examiner admitted the specification was enabling for "the fusion protein of SEQ ID NO: 4 and a composition thereof" on page 7 of the Office Action. Applicants submit that the present claims are consistent with her finding of enablement because it would not require undue experimentation for a skilled artisan to make and use the claimed invention.

Therefore, withdrawal of the enablement rejection is requested.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 23-28, 37-39 and 44-48 were rejected under Section 112, first paragraph, because they contain subject matter that allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse.

As explained above, the claimed fusion protein comprising SEQ ID NO: 4 was clearly in Applicants' possession as of the filing date. This is shown by their specification as well as the working examples.

Therefore, withdrawal of the written description rejection is requested.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The

Graham analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 23-28, 37-39 and 44-48 were rejected under Section 103(a) as allegedly unpatentable over Colombo et al. (J. Immunol. 160:2780-2785, 1998) in view of Colombo et al. (Int'l Arch. Allergy Immunol., 130:173-179, 2003), Bonura et al. (Int'l Arch. Allergy Immunol. 126:32-40, 2001) and Pauli et al. (Clin. Exp. Allergy 30:1076-1084, 2000). Applicants traverse.

Applicants' invention provides a fusion protein for use in specific immunotherapy treatment of allergies, namely allegenic constructs having a decreased ability to bind and activate IgE, but retaining (or even improving) the immunogenic capability of the wild type allergens. The decrease in binding capability is shown by low scores (%) of inhibition in a binding-inhibition ELISA assay.

Since more than one antigen actively contributes to eliciting an allergic response (e.g., both Parj1 and Parj2 contribute to inducing *Parietaria* allergy), effective treatment of allergy should be obtained using both antigens. Here, Applicants' invention uses a

fusion protein comprising amino acid sequences of two different allergens that were modified to acquire desirable properties, specifically the amino acid sequence SEQ ID NO: 4.

The binding properties of the fusion protein of claim 28 (see PjEDcys in Fig. 2) is clearly shown by the results reported in the present examples. Fusion protein PjEDcys exhibits a dramatically reduced binding capability to IgE (thus, a reduced capability of interacting with IgE and activating an immune response) as compared to the corresponding wild type heterodimer (see Fig. 5). Fig. 5 reports an average inhibition for PjEDcys of about 7.3% against 62% for the wild type allergen. PjEDcys also exhibits a reduced binding capability to IgE compared to the single muteins (monomers) PjA, PjB, PjC, and PjD[1]. Fig. 9 shows an inhibition of 14% for the best of these muteins as shown by PjC that is, however, twice as high as PjEDcys.

PjEDcys also exhibits a reduced binding capability to IgEs as compared to the mixture of wild type rParj1 and rParj2 (average inhibition 76.5%), rParj1 only (average inhibition 40.1%), or rParj2 only (average inhibition 61.1%) as reported in Fig. 8. This reduced binding to IgE is unexpectedly accompanied by enhanced immunogenic capability as shown in Fig. 7. The results reported in Fig. 7D demonstrate that PjEDcys is capable of stimulating CD3+ cells more efficiently than a mixture of separate allergens Parj1 and Parj2 (which, by the way, is shown to exhibit the highest binding ability to IgE). Therefore, the claimed fusion protein (e.g., PjEDcys) is a patentable improvement over the individual proteins separately.

These results are completely unexpected from documents cited in the rejections below. Moreover, the results reported in and derivable from the present specification are confirmed by the recent publication of Bonura et al. (Int'l Arch. Allergy Immunol. 142: 274-284, 2007; previously made of record).

It was alleged that Colombo (1998) teaches mutations in positions C4, C52, C14, C29, C30 and C75 lead to a loss of IgE binding in this region. But this is incorrect. It is

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[1] As evident from Fig. 3 of WO 02/20790 (previously made of record) PjA lacks disulphide bridges: 14-29 and 30-75; PjB lacks 50-91 and 4-52; PjC lacks 4-52, 14-29 and 30-75; and PjD lacks all four disulphide bridges.

clear from the section "Epitope Mapping" (see bottom of page 2781) that the sole Cys residues considered in Colombo are those in the 1-30 fragment. Actually, Colombo prepared only deletions or substitutions in positions 30, 29, 4 and 14 (see Fig.2A): deletion C30 (pPJ1.5), deletions C29 and C30 (pPJ1.6), substitution C4S (pPJ1.7), substitution C29S (pPJ1.8), and substitution C14S (pep3). Of these, pPJ1.5 (deletion C30) and pPj1.7 (substitution C4S) are said to be still capable of binding IgE (page 2781, last line, and page 2782, lines 1-4). Colombo also reported other mutations that result in loss of IgE binding, namely K21, K23, E24 and K27.

Therefore, Colombo does not teach or make obvious any mutation in position 52 or 75 as alleged by the Examiner. Moreover, Colombo does not teach or make obvious that mutations in position 30, 29, 14 or 4 result in loss of IgE binding. On the contrary, Colombo discloses that mutations in position 30 or 4 do not affect IgE binding. Colombo also does not disclose, or even make obvious, that the disruption of disulphide bridges is the sole means to inhibit IgE binding. Instead, a range of possible mutations including cysteine, lysine (K), and glutamic acid (E) residues are disclosed. Further, Colombo does not teach or make obvious any specific combination of modifications, such as the combination C4, C29 and C30 characterizing the fusion protein PjEDcys (see Fig. 2 and SEQ ID NO: 4). Rather, Colombo teaches away from constructs comprising modification in positions C30 or C4 because pPj1.5 (C30) and pPJ17 (C4) are still capable of binding IgE. Finally, Colombo fails to teach or make obvious any dimeric fusion protein that comprises muteins of two different allergens (e.g., Parj1 and Parj2). This difference was acknowledged by the Examiner.

Bonura corresponds to the disclosure of WO 02/20790 and teaches muteins of only the Parj1 allergen. The IgE binding activity of any single mutein PjA, PjB, PjC and PjD is analyzed, and the results are the same as those reported in Fig. 9 of the present application at issue. Bonura, like Colombo, does not teach or make obvious any heterodimer fusion protein comprising muteins of two different allergens: i.e., Parj1 and Parj2.

The Examiner asserts, however, that Pauli teaches the improved efficacy of a dimeric form of an allergen and would, therefore, suggest the construction of a dimeric

fusion protein comprising the Parj1 and Parj2 allergens as mutated according to Colombo or Bonura. This conclusion is clearly wrong.

Firstly, Pauli's experimental work relates to Bet v-1 allergen and its derivatives. But Bet v-1 and Bet v-2 are birch (*betullaceous*) tree pollen allergens that are taxonomically not related to the plants and ns-LTP allergens of Applicants' invention.

Pauli's disclosure appears to be completely immaterial as regards the claimed invention, since the results reported therein does not suggest anything concerning the activity of a group of allergens (ns-LTP) totally unrelated to birch tree allergens. There is also no other evidence of record establishing a reasonable expectation of success that one of ordinary skill in the art would have predicted the effects obtained when the modifications reported by Pauli are applied to ns-LTP allergens, nor would the same inhibition of IgE binding observed by Pauli be expected for a totally different allergen group.

Secondly, Pauli discloses derivatives (i.e., either fragments or dimers or trimers) of a single allergen: Bet v 1. Thus, one of ordinary skill in the art, by combining Colombo with Bonura and Pauli, would have prepared, at best, an allergen derivative, perhaps in modified form, free of one or more disulphide bridges, but always deriving from only one allergen: either Parj1 or Parj2. Therefore, even combining the cited documents together, one of ordinary skill in the art would not have concluded that it was obvious to prepare a heterodimeric fusion protein comprising different allergens: i.e., both Parj1 and Parj2.

Finally, Pauli not only does not make obvious the claimed invention, but actually teaches away from preparing and assaying any dimeric fusion protein. One of ordinary skill in the art is cautioned of the risk of anaphylactic side effects induced by injecting Bet v-1 wild type allergen or a derivative thereof (see page 1082, right hand column, middle paragraph, starting with "That hypoallergenic molecules can be injected . . ."). For this reason, Pauli specifically admits, "We did not include Bet v1 dimer in the intradermal tests because it proved to have a higher skin test reactivity than Bet v1 trimer in the skin pick test" (page 1082, left hand column, last paragraph). For this reason, Pauli concludes, "It is planned to prepare vaccine which consist of the two rBet v-1 fragments or rBet v-1 trimer adsorbed to Al(OH)3" (page 1082, last line, et seq.). Therefore, one of

ordinary skill in the art reading Pauli would not have found it obvious to prepare a fusion protein comprising a Bet v-1 dimer.

If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited prior art effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Moreover, if the proposed modification would change the principle of operation of the prior art invention being modified, then the cited prior art also fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Thus, Colombo and Pauli cannot be relied upon to establish a case of prima facie obviousness because the operation of Applicants' invention is incompatible with the teachings of the cited documents.

Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the improvement in the use of the claimed fusion protein in specific immunotherapy would not have been predicted from the cited documents.

Claims 23-28, 37-39 and 44-48 were rejected under Section 103(a) as allegedly unpatentable over Vrtala et al. (FASEB J. 15:2045-2047, 2001) in view of Colombo et al. (Int'l Arch. Allergy Immunol., 130:173-179, 2003), Colombo et al. (J. Immunol. 160: 2780-2785, 1998), and Bonura et al. (Int'l Arch. Allergy Immunol. 126:32-40, 2001). Applicants traverse.

Applicants' invention provides a fusion protein for use in specific immunotherapy treatment of allergies, namely allegenic constructs having a decreased ability to bind and activate IgE, but retaining (or even improving) the immunogenic capability of the wild type allergens. The decrease in binding capability is shown by low scores (%) of inhibition in a binding-inhibition ELISA assay.

Since more than one antigen actively contributes to eliciting an allergic response (e.g., both Parj1 and Parj2 contribute to inducing *Parietaria* allergy), effective treatment of allergy should be obtained using both antigens. Here, Applicants' invention uses a fusion protein comprising amino acid sequences of two different allergens that were

modified to acquire desirable properties, specifically the amino acid sequence SEQ ID NO: 4.

The binding properties of the fusion protein of claim 28 (see PjEDcys in Fig. 2) is clearly shown by the results reported in the present examples. Fusion protein PjEDcys exhibits a dramatically reduced binding capability to IgE (thus, a reduced capability of interacting with IgE and activating an immune response) as compared to the corresponding wild type heterodimer (see Fig. 5). Fig. 5 reports an average inhibition for PjEDcys of about 7.3% against 62% for the wild type allergen. PjEDcys also exhibits a reduced binding capability to IgE compared to the single muteins (monomers) PjA, PjB, PjC, and PjD[2]. Fig. 9 shows an inhibition of 14% for the best of these muteins as shown by PjC that is, however, twice as high as PjEDcys.

PjEDcys also exhibits a reduced binding capability to IgEs as compared to the mixture of wild type rParj1 and rParj2 (average inhibition 76.5%), rParj1 only (average inhibition 40.1%), or rParj2 only (average inhibition 61.1%) as reported in Fig. 8. This reduced binding to IgE is unexpectedly accompanied by enhanced immunogenic capability as shown in Fig. 7. The results reported in Fig. 7D demonstrate that PjEDcys is capable of stimulating CD3+ cells more efficiently than a mixture of separate allergens Parj1 and Parj2 (which, by the way, is shown to exhibit the highest binding ability to IgE). Therefore, the claimed fusion protein (e.g., PjEDcys) is a patentable improvement over the individual proteins separately.

These results are completely unexpected from documents cited in the rejections below. Moreover, the results reported in and derivable from the present specification are confirmed by the recent publication of Bonura et al. (Int'l Arch. Allergy Immunol. 142: 274-284, 2007; previously made of record).

Vrtala's disclosure is not substantially different from Pauli. Vrtala relates to Bet v-1 allergen. As already explained above, Bet v-1 is a birch tree (*betullaceous*) pollen allergen and is not related to the ns-LTP allergens of the present application. The cited

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[2] As evident from Fig. 3 of WO 02/20790 (previously made of record) PjA lacks disulphide bridges: 14-29 and 30-75; PjB lacks 50-91 and 4-52; PjC lacks 4-52, 14-29 and 30-75; and PjD lacks all four disulphide bridges.

document appears to be completely immaterial as regards the claimed invention, since the results reported therein does not suggest anything concerning the activity of a group of allergens (ns-LTP) totally unrelated to birch tree allergens. There is also no other evidence of record establishing a reasonable expectation of success that one of ordinary skill in the art would have predicted the effects obtained when the modifications reported by Vrtala are applied to ns-LTP allergens, nor would the same inhibition of IgE binding observed by Vrtala be expected for a totally different allergen group.

Further, Vrtala discloses dimers or trimers of a single allergen: Bet v 1. Thus, one of ordinary skill in the art, by combining Vrtala with Colombo and Bonura, would have prepared, at best, an allergen derivative, perhaps in modified form, free of one or more disulphide bridges, but always deriving from one allergen: either Parj1 or Parj2. Therefore, even combining the three cited documents together, one of ordinary skill in the art would not have concluded from the evidence of record that it was obvious to prepare a heterodimeric fusion protein comprising different allergens: i.e., both Parj1 and Parj2.

In any case, Vrtala, like Pauli, focuses on a trimer rather than a dimer of Bet v1 allergen. This is evident not only from the title, but also from the section "Conclusions" that are totally silent on any reason to prepare the dimer. The reason resides in the fact that the dimer is much less preferred than the trimer for use because the former induces a higher skin reaction and allergic activity when compared to the latter. This is shown in the results reported in section "Recombinant Bet v1 trimer exhibits profoundly reduced allergic activity" on page 2045. The mean wheal diameters of the skin reaction area (at 10 µg/ml) is 4.1 ± 2.4 (dimer) vs. 0.7 ± 1.2 (trimer) and (at 100 µg/ml) 7.3 ± 2.5 (dimer) vs. 3.6 ± 2.1 (trimer). These results confirm the previously discussed prior art's teaching away from Applicants' invention, and would have further contributed to dissuading one of ordinary skill in the art from considering the dimeric form as a valid tool for preparing a vaccine for immunotherapy.

If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited prior art effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Moreover, if the proposed modifi-

cation would change the principle of operation of the prior art invention being modified, then the cited prior art also fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959). Thus, Vrtala and Colombo cannot be relied upon to establish a case of prima facie obviousness because the operation of Applicants' invention is incompatible with the teachings of the cited documents.

Finally, the Examiner is required to consider whether the improvement obtained by the present invention is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396. In Applicants' invention, the improvement in the use of the claimed fusion protein in specific immunotherapy would not have been predicted from the cited documents.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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